REMARKS

Claims 1-20 are pending in the application. Claims 12, 13 and 18-20 are withdrawn from consideration. Claims 1-11, 14-16 and 20 are currently being examined. Claims 1-5, 8-9, 11, 15-16 and 20 have been amended to clarify the subject matter Applicants regard as their invention. Specifically, claim 1 has been amended to narrow the definitions for R_1 and R_4, which have been recited in original claims 2 and 5, respectively. No new matter has been introduced through these amendments.

Claim Objections

Claim 1 is objected to for the recitation of the phrase "where the substituents have the following meaning." Based on the Examiner's suggestion, Applicants have replaced the phrase with the term "wherein," and therefore, the objection is moot.

Claim Rejections Under 35 U.S.C. § 112, ¶1

Claim 14

Claim 14 is rejected under 35 U.S.C. § 112, ¶1, as failing to comply with the enablement requirement. Claim 14 is directed to a pharmaceutical composition for use in the treatment of tumors containing one or more compounds of the present invention. The Examiner has alleged that while claim 14 reciting the term "pharmaceutical composition," the specification fails to teach "how to use the compounds of the invention to therapeutic effect *for any condition*" (emphasis added). *See* the Office Action, page 3. Applicants respectfully disagree.

According to Manual of Patent Examining Procedure ("MPEP"), § 2164.04, "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." Also *see In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of the

protection provided by a claim is not adequately enabled by the disclosure). However, the Examiner has not provided a reasonable explanation as to why the specification fails to teach one of skill in the art to use the compounds of the invention "for any condition." Further, given the experimental data provided in the specification, *i.e.*, Example 18 (*in vitro* testing the compounds of the invention[1] for inhibition of the proliferation of various tumor cell lines) and Example 19 (*in vitro* testing the compounds of the invention for inhibition of the polymerization of tubulin), the specification at least teaches one of skill in the art to use the compounds of the invention to inhibit tumor cell lines or inhibit tubulin polymerization. Therefore, the Examiner has not met his initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.

Furthermore, Applicants would like to point out that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Here, Applicants not only provide general guidance on the use of the compounds of the invention for the treatment of benign and malignant tumors (*see* paragraphs [0003] and [0065]-[0067]), but also present specific examples for *in vitro* testing the compounds of the invention for inhibition of the proliferation of various tumor cell lines (*see* Example 18) and for *in vitro* testing the compounds of the invention for inhibition of the polymerization of tubulin (*see* Example 19). "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." *See* MPEP §2164.02. Thus, one person skilled in the art, provided with the general guidance and specific examples in the

[1] Compounds 14-16 are pyrazole compounds elected for examination.

specification directed against a variety of tumors, would have a reasonable expectation that a pharmaceutical composition containing the compounds of the invention would have efficacy in a variety of abnormal tumorous disorders. Moreover, when the artisan is fully able to utilize claimed subject matter as described in the specification, clinical testing should not be made a prerequisite to patentability. *See In re Hartop*, 311 F.2d 249 (CCPA 1962) and *Ex parte Rubin*, 5 USPQ 2d 1461 (BPAI 1987).

In addition, Applicants submit herewith additional *in vitro* testing on various tumor models with the claimed compounds. See Exhibit A.

For at least the foregoing reasons, Applicants submit claim 14 is enabled.

Claim 1

Claim 1 is rejected under 35 U.S.C. § 112, ¶1, for lack of enablement. The Examiner has alleged that the specification, "while being enabling for other forms, does not reasonably provide enablement for solvates." Applicants has deleted the term "solvates" from claim 1, and thus, the rejection is moot and can be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, ¶2

Claims 1-11

Claims 1-11 are rejected under 35 U.S.C. § 112, ¶2, for being indefinite for containing quotation marks. Applicants have deleted those quotation marks, and therefore, this rejection has been overcome.

Claim 2

Claim 2 rejected under 35 U.S.C. § 112, ¶2, for being indefinite for reciting phrase "such as." Applicants have replaced the phrase "such as" with the phrase "selected from the group consisting of," and therefore, this rejection has been overcome.

Claims 3-4

Claims 3-4 are rejected under 35 U.S.C. § 112, ¶2, for being indefinite for reciting "claims 1."[2] Applicants have replaced "claims 1" with "claim 1," and therefore, this rejection has been overcome.

Claims 1, 9, 15, 16 and 20

Claims 1, 9, 15, 16 and 20 are rejected under 35 U.S.C. § 112, ¶2, for being indefinite for reciting the term "tolerable." Applicants have deleted the term, and therefore, this rejection has been overcome.

Claim 11

Claim 11 is rejected under 35 U.S.C. § 112, ¶2, for being indefinite for lack of a period. Applicants have added a period, and therefore, this rejection has been overcome.

Claim Rejections Under 35 U.S.C. § 102

Ermandi *et al.*

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 102(b), as being anticipated by Ermandi *et al.* (Farmaco Ed. Sci., 53 (1998) 519-524).

The broadest compound claim 1, as amended, is directed to a class of pyrazole-substituted carbonylpiperazines, wherein the piperazine ring cannot be substituted with a quinazolinyl group. All of the compounds disclosed in Ermandi *et al.* have a quinazolinyl group substituted on the piperzine ring. Thus, the compounds of amended claim 1 are different from those disclosed in Ermandi *et al.* Accordingly, Ermandi *et al.* cannot anticipate claim 1 as presently amended.

[2] Applicants have also amended claims 5 and 8 for the same typographical error.

Claims 2-11, 15-16 and 20 either depend from claim 1 or recite the compounds of claim 1. For the reasons set forth above with respect to claim 1, Ermandi *et al.* cannot not anticipate any of claims 2-11, 15-16 and 20.

Zhu *et al.*

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 102(b), as being anticipated by Zhu *et al.* (WO 01/19798).

The broadest compound claim 1, as amended, is directed to a class of pyrazole-substituted carbonylpiperazines, wherein the pyrazole ring can be substituted with heteroaryl, phenyl, and anthracenyl groups.

Zhu *et al.* disclose a broad genus of compounds useful for treating or preventing coagulation disorders. However, Zhu *et al.* do not teach any specific species that falls within the scope of amended claim 1. Further, the broad genus disclosed in Zhu *et al.* overlaps with the genus of claim 1 since in the Zhu's genus, the substitute (X) on a heteroaryl (G, *e.g.*, pyrazole) cannot be an anthracenyl group, while the compounds of amended claim1 can have such a substitute. Therefore, Zhu *et al.* cannot anticipate claim 1 as presently amended.

Claims 2-11, 15-16 and 20 either depend from claim 1 or recite the compounds of claim 1. For the reasons set forth above with respect to claim 1, Zhu *et al.* cannot anticipate any of claims 2-11, 15-16 and 20.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Zhu *et al.* (WO 01/19798). Applicants respectfully traverse this rejection.

The broadest compound claim 1, as amended, is directed to a class of pyrazole-substituted carbonylpiperazines, wherein the pyrazole ring can be substituted with heteroaryl, phenyl, and anthracenyl groups.

According to the Examiner, the compounds of claim 1 are a "more limited genus" (*i.e.*, a subgenus) of the genus disclosed in Zhu *et al.*, and thus it would have been obvious to one of skill in the art to select any of the species of the genus taught by Zhu *et al.* because "the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties, and thus, the same use as taught for the genus as a whole." *See* the Office Action, page 7.

However, first of all, the compounds of amended claim 1 are *not* a subgenus of the genus disclosed in Zhu *et al.* As discussed above, in the genus disclosed in Zhu *et al.*, the substitute (X) on a heteroaryl (G, *e.g.*, pyrazole) cannot be an anthracenyl group, while the compounds of claim 1 can have such a substitute. Even the compounds of amended claim 1 are a subgenus, the fact that a claimed subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird,* 16 F.3d 380, 382 (Fed. Cir. 1994)("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). The size of the genus disclosed in Zhu *et al.* is extremely large, and there is no teaching or suggestion which of the possibilities corresponds to the claimed pyrazole-substituted carbonylpiperazines. *In re Bell,* 991 F.2d 781, 784 (Fed. Cir. 1993) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."). Similarly here, one of skill in the art, without any teaching or suggestion, would have not expected that any

species in such a size of the Zhu's genus would have similar properties, and therefore would have not been able to choose a subgenus of the claimed pyrazole-substituted carbonylpiperazines for further studies.

Furthermore, while the compounds disclosed in Zhu *et al.* useful for treating or preventing coagulation disorders, the compounds of amended claim 1 have the properties of treating tumors. *In re Albrecht*, 514 F.2d 1389, 1392 (CCPA 1975) ("the prior art compound so irritated the skin that it could not be regarded as useful for the disclosed anesthetic purpose, and therefore a person skilled in the art would not have been motivated to make related compounds."). Similarly here, Zhu *et al.* would not provide any motivation to one of skill in the art to make a subgenus of the disclosed compounds.

Accordingly, the Examiner has not met his burden of establishing a *prima facie* case of obviousness.

In addition, Applicants would like to direct the Examiner's attention to the description provided in the specification. The specification provides that it has surprisingly found that novel compounds of the invention are suitable for the treatment of benign and malignant tumors (*see* paragraph [0010]), and that the *in vitro* testing results show a very potent inhibition of the proliferation of selected tumor cell lines (*see* paragraph [0146]). Therefore, even a *prima facie* case of obviousness had been established by the Examiner, it can be rebutted by the unexpected findings provided in the specification.

For the reasons set forth above, there is neither any disclosure nor any suggestion in Zhu *et al.* that would have rendered claim 1 obvious. By the same token, 2-11, 15-16 and 20, which include all the limitations of claim 1, are also not rendered obvious by Zhu *et al.*

Applicants accordingly request that the rejection of claims 1-11, 15-16 and 20 under 35 U.S.C. § 103 be withdrawn.

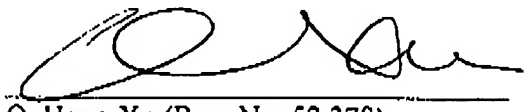
CONCLUSION

In light of the foregoing, Applicants respectfully submit that all claims are now in condition for allowance.

Applicants submit herewith authorization to charge fees associated with the accompanying the Petition for Extension of Time. It is believed that no other fees are necessitated by the present Reply. However, in the event that any additional fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-0923.

If the Examiner believes that a telephone conversation with Applicants' attorney would expedite allowance of this application, the Examiner is cordially invited to telephone the undersigned attorney at the number provided below.

Respectfully submitted,



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